Second Cancers Among 40 576 Testicular Cancer Patients: Focus on Long-term Survivors

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Background: **Although second primary cancers are a leading cause of death among men with testicular cancer, few studies have quantified risks among long-term survivors.** ***Methods:*** **Within 14 population-based tumor registries in Europe and North America (1943–2001), we identified 40 576 1-year survivors of testicular cancer and ascertained data on any new incident solid tumors among these patients. We used Poisson regression analysis to model relative risks (RRs) and excess absolute risks (EARs) of second solid cancers. All statistical tests were two-sided.** ***Results:*** **A total of 2285 second solid cancers were reported in the cohort. The relative risk and EAR decreased with increasing age at testicular cancer diagnosis ($P<.001$); the EAR increased with attained age ($P<.001$) but the excess RR decreased. Among 10-year survivors diagnosed with testicular cancer at age 35 years, the risk of developing a second solid tumor was increased (RR = 1.9, 95% confidence interval [CI] = 1.8 to 2.1). Risk remained statistically significantly elevated for 35 years (RR = 1.7, 95% CI = 1.5 to 2.0; $P<.001$). We observed statistically significantly elevated risks, for the first time, for cancers of the pleura (malignant mesothelioma; RR = 3.4, 95% CI = 1.7 to 5.9) and esophagus (RR = 1.7, 95% CI = 1.0 to 2.6). Cancers of the lung (RR = 1.5, 95% CI = 1.2 to 1.7), colon (RR = 2.0, 95% CI = 1.7 to 2.5), bladder (RR = 2.7, 95% CI = 2.2 to 3.1), pancreas (RR = 3.6, 95% CI = 2.8 to 4.6), and stomach (RR = 4.0, 95% CI = 3.2 to 4.8) accounted for almost 60% of the total excess. Overall patterns were similar for seminoma and nonseminoma patients, with lower risks observed for nonseminoma patients treated after 1975. Statistically significantly increased risks of solid cancers were observed among patients treated with radiotherapy alone (RR = 2.0, 95% CI = 1.9 to 2.2), chemotherapy alone (RR = 1.8, 95% CI = 1.3 to 2.5), and both (RR = 2.9, 95% CI = 1.9 to 4.2). For patients diagnosed with seminomas or nonseminomatous tumors at age 35 years, cumulative risks of solid cancer 40 years later (i.e., to age 75 years) were 36% and 31%, respectively, compared with 23% for the general population.** ***Conclusions:*** **Testicular cancer survivors are at statistically significantly increased risk of solid tumors for at least 35 years after treatment. Young patients may experience high levels of risk as they reach older ages. The statistically significantly increased risk of malignant mesothelioma in testicular cancer survivors has, to our knowledge, not been observed previously in a cohort of patients treated with radiotherapy. [J Natl Cancer Inst 2005;97:1354–65]**

Testicular cancer is a curable malignancy, with a 10-year relative survival rate of up to 95% *(1,2)*. Because this cancer largely affects young men, a resultant lifetime exists for manifestation of the late effects of treatment, including new malignant neoplasms. Second primary cancers have emerged as a leading cause of death among testicular cancer survivors *(3–5)*, although few studies have quantified long-term risk. Several investigations *(6–9)* describe increased risks of second cancer in testicular cancer patients with up to 10–20 years of follow-up, but not beyond. It is thus not known whether excess risks persist for longer periods or even whether they may eventually decrease. Moreover, estimates of the excess absolute risk of second malignant neoplasms are not available, and the effect of age at initial treatment and of attained age (age at observation) on cancer risk has not been examined. Although radiotherapy field sizes and treatment doses have been reduced in recent years *(10,11)*, considerable numbers of testicular cancer patients treated in the past with more aggressive radiotherapy approaches remain at long-term risk for second cancers *(9)*. The heightened concern regarding the role of chemotherapy for testicular cancer in the development of solid tumors, which has been analyzed only in small series of patients with relatively short follow-up times *(7,8,12)*, also merits further investigation. In this study, we quantify the long-term site-specific absolute and relative risks of incident solid cancers among more than 40 000 1-year survivors of testicular cancer reported to population-based cancer registries in Europe and North America.

Patients and Methods

Patients

Men diagnosed with a first primary cancer of the testis between January 1, 1943, and December 31, 2001, and who

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survived at least 1 year (n = 40 576 patients), were ascertained within 14 population-based cancer registries in Canada (Ontario, inclusive period from 1964 through 2000), Denmark (from 1943 through 1998), Finland (from 1953 through 2001), Norway (from 1953 through 1999), Sweden (from 1958 through 2001), and the United States (from 1973 through 1999) *(13)*. In the United States, patients were identified in nine registries that participate in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, which covers approximately 10% of the population and includes the states of Connecticut (from 1973), Hawaii (from 1973), Iowa (from 1973), New Mexico (from 1973), and Utah (from 1973), as well as the metropolitan areas of San Francisco–Oakland (from 1973), Detroit (from 1973), Seattle–Puget Sound (from 1974), and Atlanta (from 1975). A subset of patients with testicular cancer described in previous reports *(6,8,9,14)* are included, with extended follow-up.

Participating cancer registries collect data on patient demographic characteristics, tumor histology, and vital status. Three major histologic groups of testicular cancer were identified: seminomatous and nonseminomatous germ cell tumors and cancers of other or unspecified histologic type. Patients with extragonadal germ cell tumors or testicular lymphomas were excluded. All registries, except those in Sweden and Ontario, compile information on initial type of cancer therapy, expressed in general categories. With these data, testicular cancer patients whose primary therapy included radiotherapy and/or chemotherapy were identified. Registries record data on initial, but not subsequent, courses of treatment, and details of specific treatment regimens, including radiotherapy fields, are not available in registry files. The known underreporting of treatment to cancer registries *(15)* precluded identification of a definitive reference group of patients treated with surgery only, because this latter group may have received radiotherapy or chemotherapy as subsequent or salvage treatment.

Standard management of testicular cancer includes orchiectomy, with adjuvant regional radiotherapy or retroperitoneal lymph node dissection used for early-stage seminomas or nonseminomatous germ cell tumors, respectively *(16)*. When adjuvant radiotherapy was given in the past, infradiaphragmatic fields included para-aortic and pelvic lymph node areas, with larger doses (45–55 Gy) given to treat nonseminomatous germ cell tumors than to treat seminomas (25–35 Gy) *(17,18)*. More recently, fields limited to the para-aortic lymph nodes have been used to treat seminomas, and radiation doses have been reduced to 20 Gy *(10,11,19)*. Average doses of radiation received by several organs during simulated, standard radiotherapy techniques for testicular cancer, including chest irradiation *(20)*, which is no longer used, are shown in Appendix Table 1. Since the 1970s, an increasing percentage of nonseminoma patients has been managed with retroperitoneal lymph node dissection and chemotherapy instead of radiotherapy, whereas radiotherapy has remained the standard treatment for seminoma. Since the mid-1970s, patients with advanced testicular cancer have received combination chemotherapy that includes cisplatin, vinblastine, and bleomycin, with etoposide being used since the 1980s *(23)*. In prior years, cytotoxic therapy included cyclophosphamide, dactinomycin, mithramycin, vinblastine, and bleomycin *(6,8,12,24)*.

Invasive solid cancers diagnosed at least 1 year after testicular cancer were identified through a search of cancer registry incidence files. Diagnoses of contralateral testicular cancer were excluded from analysis, because they were not uniformly registered by all centers. The follow-up period began 1 year after the date of testicular cancer diagnosis and ended on the date of death, date of diagnosis of a second cancer, or the study end date (December 31, 2002), whichever occurred first. (Study end dates varied slightly according to registry: December 31, 1999, for Denmark; December 31, 2000, for the SEER Program; December 31, 2001, for Ontario; and December 31, 2002, for Finland and Sweden.) Thus, because date of second cancer diagnosis served as a study endpoint, third- or higher-order cancers (n = 242 cancers in 192 patients) were not included in the analysis.

Statistical Methods

Person-years and second cancers were categorized by histologic type of testicular cancer (seminoma, nonseminoma, or other), calendar year of testicular cancer diagnosis (1943–1974 or 1975–2001), initial treatment (radiotherapy alone, chemotherapy alone, or radiotherapy and chemotherapy), and registry and by 5-year intervals of attained age, attained calendar year, time since testicular cancer diagnosis, and age at testicular cancer diagnosis. Cancer incidence rates specific for each registration area, male sex, and 5-year age and calendar year intervals were multiplied by the accumulated person-years at risk to estimate the number of cancer cases expected in each stratum.

In general, O and E were used to denote observed and expected numbers of incident second cancers. $O_{ax,a,k}$ and $E_{ax,a,k}$ were used to denote, respectively, observed and expected incident cases in a specified category identified by age at testicular cancer diagnosis (ax), attained age (a), and other variables of interest (k). Analyses that treated attained age, time since diagnosis, and age at diagnosis as continuous variables were based on midpoints of 5-year intervals. For example, the attained age group of 60–64 years was assigned a value of 62.5.

Analyses were based on Poisson regression methods, in which it is assumed that the number of incident solid cancers follows a Poisson distribution with mean given by the product of the person-years and the cause-specific incidence rate for each cell of a multiway person-year table *(25–30)*. Parameter estimates were computed with maximum likelihood methods. Hypothesis tests and confidence intervals (CIs) were based on likelihood ratio tests and direct evaluation of the profile likelihood. The 95% confidence intervals shown in Appendix Table 2 were calculated as described previously by Liddell *(31)*. Two-sided P values are used throughout. Analyses were implemented with the AMFIT module of the software package EPICURE *(32)*.

Both the excess relative risk (ERR) and excess absolute risk (EAR) were evaluated. The ERR was defined as RR – 1, where RR denotes the ratio of risk in testicular cancer patients to that in the general population. A simple unadjusted estimate of the RR is the O/E ratio. The EAR was defined as the difference in risks between testicular cancer patients and the general population and is expressed as the number of excess cases per 10 000 person-years. The RR is the usual measure for etiologic research and the measure that has been emphasized in most previous studies addressing second cancers. However, the EAR is a useful measure for estimating the absolute burden or magnitude of a

health problem *(33)*. A simple unadjusted estimate of the EAR is $(O - E)/10\,000$ person-years. The expected value of $O_{ax,a,k}$ was assumed to be

$E_{ax,a,k}[1 + \mathrm{ERR}(ax,a,k)]$, for the ERR model, and
$E_{ax,a,k} + \mathrm{EAR}(ax,a,k)$, for the EAR model.

Results presented in Fig. 1 express the ERR and EAR as continuous functions of age at testicular cancer diagnosis (ax) and attained age (a) by use of the expression below:

$$\mathrm{ERR}(ax,a) \text{ or } \mathrm{EAR}(ax,a) = \theta \exp[\beta_1(ax - 35) + \beta_2 \log(a/60)]. \quad \text{[Eq. 1]}$$

The parameter θ is scaled so that it represents the ERR or EAR at the attained age of 60 years for a patient diagnosed at age 35 years. The form of the model shown in Eq. 1 was selected because it has been used to model risks in other radiation-exposed cohorts *(29,30)*. The fit of this model was checked by comparing its deviance to models that estimated the ERR or EAR for categories defined by age at testicular cancer diagnosis and attained age.

Results were adjusted for age at testicular cancer diagnosis (see Tables 3 and 4). For these analyses, the expected value of $O_{ax,k}$ was assumed to be

$$E_{ax,k}[1 + \mathrm{ERR}(ax,k)], \text{ with } \mathrm{ERR}(ax,k) = \theta_k \exp[\beta(ax - 35)], \quad \text{[Eq. 2]}$$

where k indexes categories defined by histologic type of testicular cancer, time since testicular cancer diagnosis, initial treatment, and calendar year of testicular cancer diagnosis. With this formulation, θ_k represents the ERR for a patient diagnosed with testicular cancer at age 35 years, which is the average age of the cohort. For analyses of site-specific cancers (see Table 4), we fixed the value of β to be that estimated for all solid cancers (-0.054) but tested whether data were compatible with this value, so that the ratios of ERRs for different cancer sites would be the same for all ages at testicular cancer diagnosis. Unless otherwise specified, tables and text present relative risks for patients diagnosed at age 35 years; these data were obtained as $1 + \theta_k$. The dependence of the ERR (and RR) on age at diagnosis is not meaningful when the ERR is negative (i.e., RR < 1). Thus, when such results occurred as lower confidence bounds, they are reported simply as "<1." The number of excess cancers was estimated as the sum over all cells of the terms $E_{ax,k}$ $\mathrm{ERR}_{(ax,k)}$.

Preliminary analyses revealed statistically significant heterogeneity of risk for all second solid cancers among the six countries ($P<.001$), resulting from lower risks for the SEER Program and Ontario and which are likely related to migration from registry catchment areas. For this reason, the expressions in Eq. 1 were multiplied by an estimated adjustment factor, $\exp(\lambda r)$, where the variable $r = 1$ for North American registries (SEER Program and Ontario) and latency of 10 years (see below) or more or $r = 0$ otherwise. The factor $\exp(\lambda)$ was estimated to be about 0.7 in analyses of all solid cancers. Exploration of this adjustment indicated that, after 10 years of follow-up, this factor did not depend further on time since testicular cancer diagnosis, on age at testicular cancer diagnosis, or on attained age. After the adjustment was applied, there was no further evidence of heterogeneity among the six major registries ($P>.5$).

Because there is a minimum latency interval associated with excess solid tumors related to antecedent cancer treatment and because the focus of this paper is on long-term survivors, most analyses were restricted to periods of 10 years or more after testicular cancer diagnosis. The most detailed analyses focus on all solid cancers as a single category. A combined group of in-field sites (stomach, small intestine, colon, rectum, liver, gallbladder and ducts, pancreas, kidney, and bladder) that are likely to receive the highest radiation doses during infradiaphragmatic radiotherapy for testicular cancer (Appendix Table 1) was also evaluated. Less detailed analyses of site-specific cancers were also conducted.

Analyses comparing solid cancer risks for testicular cancer patients diagnosed before and after 1975 (see Table 3) were restricted to the 10- to 24-year period after testicular cancer diagnosis because few patients diagnosed after 1975 were followed for more than 25 years. Because data collection in the SEER Program did not begin until 1973, these patients were excluded from this set of analyses.

Cumulative probabilities of developing second solid cancers were calculated with an approach similar to that used for estimating lifetime risks from radiation exposure *(31)*. The approach takes into account the dependency of absolute risks on both age at testicular cancer diagnosis and attained age and dependency on competing risks from testicular cancer mortality, noncancer mortality, and any intervening diagnosis of leukemia, lymphoma, or other nonsolid cancer. The cumulative probability $CUM(ax,t)$ for a person diagnosed at age ax at t years after exposure (at attained age $a = ax + t$) was calculated as follows: $CUM(ax,t) = \sum_a [SC(a) + M(ax\ a)]S(a|ax)$, where the summation is from $a = ax + 1$ to $ax + t$. $SC(a)$ is the baseline risk of solid cancers and $M(ax,a)$ is the expression for the EAR of second cancer based on the model (Fig. 1, B). $S(a|ax)$ is the probability of surviving free of a second cancer to age a, conditional on such survival to age ax. Separate calculations were made for seminoma and nonseminoma patients.

Estimating $S(a|ax)$ required estimating risks of second cancer incidence, noncancer mortality (NC), testicular cancer mortality (TC), nonsolid cancer incidence (NS), and excess leukemia (LK) for each attained age a. $S(a|ax)$ was then estimated as follows: $S(a = ax + 1|ax) = 1$ and $S(a + 1|ax) = S(a|ax)\,[1 - SC(a) - M(ax,a) - NC(a) - TC(ax,a,t) - NS(a) - LK(t)]$. $SC(a)$, $NC(a)$, and $NS(a)$ were obtained as the average (weighted by person-years) baseline rates of solid cancer incidence and noncancer mortality, respectively, for all registries from 1975 through 2001. $LK(a)$ and $TC(ax,a,t)$ were estimated by modeling leukemia incidence (103 incident cases) and testicular cancer mortality data from 1975 through 2001 (i.e., 2543 deaths).

Results

The study population consisted of 40 576 1-year survivors of testicular cancer diagnosed at an average age of 35 years (range = <1 year to 93 years). The average follow-up time was 11.3 years, with 20 984, 7885, and 2065 patients followed for 10, 20, and 30 years, respectively (Table 1). Most testicular cancers (97%) were germ cell tumors.

Second solid cancers were diagnosed in 2285 patients, but only 1619 cancers were expected ($O/E = 1.41$; 95% CI = 1.35

Table 1. Description of population-based cohort of 40 576 1-year survivors of testicular cancer*

Characteristic	No. of patients	Person-years of follow-up†	No. of second solid tumors‡
All patients	40 576	458 383	2285
GCT, seminoma§	22 424	262 162	1694
GCT, nonseminoma‖	16 776	182 313	523
Other or unspecified histology	1376	13 908	68
Age at testicular cancer diagnosis			
<30 y	14 901	173 156	339
30–39 y	14 263	163 500	673
≥40 y	11 412	121 727	1273
Calendar year of testicular cancer diagnosis			
1943–1974	6639	138 333	1202
1975–2001	33 937	320 049	1083
Population-based cancer registry			
U.S. SEER Program (1973–1999)¶	13 530	127 004	442
Denmark (1943–1998)	7879	103 300	670
Sweden (1958–2001)	6157	78 413	428
Ontario (1964–2000)	6235	71 379	284
Norway (1953–1999)	4934	57 717	348
Finland (1953–2001)	1841	20 570	113
Initial treatment#			
GCT, seminoma			
Radiotherapy, no chemotherapy	10 534	132 039	931
Chemotherapy, no radiotherapy	808	5083	17
Radiotherapy and chemotherapy	332	3342	22
Other/unspecified	220	2606	19
GCT, nonseminoma			
Radiotherapy, no chemotherapy	1944	30 653	185
Chemotherapy, no radiotherapy	3799	32 234	53
Radiotherapy and chemotherapy	450	4446	12
Other/unspecified	247	2930	11
No. of patients entering follow-up interval			
1–4 y	40 576	138 113	233
5–9 y	30 001	126 664	358
10–19 y	20 984	137 506	802
20–29 y	7885	43 701	563
30–34 y	2065	7450	169
≥35 y	1014	4948	160

*All patients were diagnosed with testicular cancer as a first primary cancer and survived 1 year or more. Of the 40 576 patients, 39 818 (98.1%) were white, 262 (0.6%) were black, and 496 (1.2%) were from other racial–ethnic groups; 2269, nine, and eight solid cancers were diagnosed in these respective groups. GCT = germ cell tumor; SEER = Surveillance, Epidemiology, and End Results.

†Mean follow-up was 11.7 years and 10.9 years for men with seminomatous and nonseminomatous GCT, respectively. Due to rounding, numbers may not sum to totals.

‡Numbers exclude contralateral testicular cancers.

§International Classification of Diseases (ICD)-0 *(35)* morphology codes 9060–9063.

‖ICD-0 *(35)* morphology codes 9070–9073, 9080–9085, and 9100–9102.

¶Calendar years of diagnosis of testicular cancer.

#Numbers include only those patients with seminomatous or nonseminomatous GCT reported to registries that collect data on initial course of cancer treatment (SEER Program, Denmark, Finland, and Norway). Data on subsequent therapy were not available in the registry records. The initial course of treatment for patients for whom the histologic type of testicular cancer was either designated as non-GCT or was not specified included radiotherapy, no chemotherapy (n = 192); chemotherapy, no radiotherapy (n = 236); radiotherapy and chemotherapy (n = 17), and other/unspecified (n = 61).

to 1.47) (Appendix Table 2). Among 10-year survivors, solid cancers were diagnosed in 1694 patients (O/E = 1.55; 95% CI = 1.48 to 1.62). Table 2 shows the number of solid tumors, the O/E ratios, and the $O - E$ differences (per 10 000 person-years) by categories of age at testicular cancer diagnosis and attained age for 10-year survivors. Both measures decreased with increasing age at diagnosis within separate attained age categories.

To describe these patterns more effectively, the ERR and EAR for solid cancers in 10-year survivors were expressed as a function of age at testicular cancer diagnosis and attained age. A strong decrease with increasing age at testicular cancer diagnosis was observed for both the ERR and EAR (P<.001) (Fig. 1). The EAR increased sharply with attained age (P<.001) (Fig. 1, B), but the ERR decreased with attained age (P = .004) (Fig. 1, A), indicating that the increase in the EAR with attained age was less than that for the baseline risks. Parameters quantifying the effect of age at testicular cancer diagnosis and attained age were similar for seminoma and nonseminoma patients (P>.5). For the ERR model, the parameter β in Eq. 2 was estimated as −0.054 (95% CI = −0.066 to −0.042), representing a nearly threefold increase in solid cancer risk for every 20-year decrease in age at testicular cancer diagnosis.

The estimated relative risks for all solid cancers are shown in Tables 3 and 4 for men diagnosed with testicular cancer at age 35, the mean age of the cohort. Relative risks increased with increasing time since testicular cancer diagnosis (P = .014) when evaluated over the entire follow-up period (Table 3). Relative risks in the periods of 1–4 years and 5–9 years were statistically significantly (P<.001) lower than those of 10 years or more since

Table 2. Second cancers among 10-year survivors of testicular cancer according to age at testicular cancer diagnosis and attained age (age at observation)

Attained age	No. of observed solid cancers by age at testicular cancer diagnosis				Observed-to-expected ratio (95% confidence interval) by age at testicular cancer diagnosis				Observed minus expected (per 10 000 person-years) by age at testicular cancer diagnosis			
	<30 y	30–39 y	≥40 y	All ages	<30 y	30–39 y	≥40 y	All ages	<30 y	30–39 y	≥40 y	All ages
<50 y	141	96	0	237	2.6 (2.2 to 3.0)	2.1 (1.7 to 2.5)	—*	2.3 (2.1 to 2.6)	14	16	—*	14
50–59 y	92	200	122	414	2.8 (2.2 to 3.4)	1.6 (1.4 to 1.8)	1.5 (1.2 to 1.8)	1.7 (1.5 to 1.9)	72	25	25	33
60–69 y	49	198	338	585	2.1 (1.6 to 2.7)	1.9 (1.6 to 2.1)	1.3 (1.1 to 1.4)	1.5 (1.4 to 1.6)	126	102	34	59
≥70 y	9	78	371	458	1.4 (0.7 to 2.5)	1.7 (1.3 to 2.1)	1.2 (1.1 to 1.4)	1.3 (1.2 to 1.4)	81	146	56	69
All ages	291	572	831	1694	2.5 (2.2 to 2.8)	1.8 (1.6 to 1.9)	1.3 (1.2 to 1.4)	1.5 (1.5 to 1.6)	—†	—†	—†	—†

*Estimate not provided because there are no person-years in this category.

†Because of the especially strong dependence of the excess absolute risk on attained age, estimates for all ages combined are not meaningful without adjustment for this variable.

diagnosis. Among 10-year survivors diagnosed at age 35 years, the relative risk was 1.9 (95% CI = 1.8 to 2.1). Risk remained statistically significantly elevated for 35 years (RR = 1.7, 95% CI = 1.5 to 2.0; $P<.001$). During the period of 10 years or more from testicular cancer diagnosis, the relative risks declined with either attained age ($P = .004$) or time since diagnosis ($P = .007$) when evaluated separately; these declines persisted when analyses were restricted to patients diagnosed before 1975. Relative risks, however, remained statistically significantly elevated in 35-year survivors ($P<.001$). Seminoma patients had slightly higher relative risks than nonseminoma patients ($P = .088$) and higher EAR, which by the attained age of 60 years was 67 per 10 000 person-years (95% CI = 57 to 77 per 10 000 person-years) for seminoma patients and 52 per 10 000 person-years (95% CI = 40–65 per 10 000 person-years) for nonseminoma patients (difference = 15 per 10 000 person-years; 95% CI = −0.2 to 29; P for difference = .053).

Among testicular cancer patients who survived at least 10 years, statistically significantly increased risks of solid cancers were associated with radiotherapy alone (RR = 2.0, 95% CI = 1.9 to 2.2), with chemotherapy alone (RR = 1.8, 95% CI = 1.3 to 2.5), and with both (RR = 2.9, 95% CI = 1.9 to 4.2) (Table 3). Risk after radiotherapy and chemotherapy was higher than risk after radiation alone ($P = .10$) or chemotherapy alone ($P = .08$). For patients given radiotherapy alone, risks were 1.1 (95% CI = <1 to 1.6), 1.5 (95% CI = 1.2 to 1.9), and 2.0 (95% CI = 1.9 to 2.2), respectively, in the follow-up periods of 1–4, 5–9, and 10 years or more.

For seminoma patients, the relative risk of solid cancers was higher for those diagnosed 1975 and later (RR = 2.3, 95% CI = 2.0 to 2.7) than for those diagnosed before 1975 (RR = 1.9; 95% CI = 1.6 to 2.1) (difference = 0.5, 95% CI for difference = 0.05 to 0.9; P for difference = .03) (Table 3). For nonseminoma patients, however, the pattern was reversed, with a particularly striking difference when the comparison was limited to patients treated with radiation only and to sites in infradiaphragmatic radiation therapy fields (RR = 1.4, 95% CI = <1 to 2.9, and 4.0, 95% CI = 2.8 to 5.3, respectively; difference = −2.6, 95% CI = <−3 to −0.7; P for difference = .01). With few testicular cancer patients receiving chemotherapy before 1975 (152 patients and seven solid cancers), meaningful comparisons by calendar year for other treatment groups were not possible.

We observed statistically significantly elevated risks, to our knowledge for the first time, for cancers of the pleura (malignant mesothelioma; RR = 3.4, 95% CI = 1.7 to 5.9) and esophagus (RR = 1.7, 95% CI = 1.0 to 2.6) (Table 4). Cancers of the lung (RR = 1.5, 95% CI = 1.2 to 1.7), colon (RR = 2.0, 95% CI = 1.7 to 2.5), bladder (RR = 2.7, 95% CI = 2.2 to 3.1), pancreas (RR = 3.6, 95% CI = 2.8 to 4.6), and stomach (RR = 4.0, 95% CI = 3.2

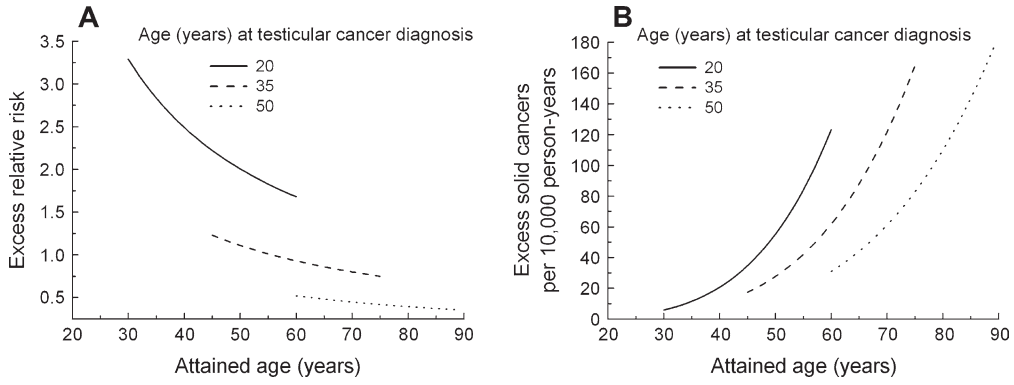

Fig. 1. Excess relative risk (ERR) and excess absolute risk (EAR) of second solid cancers among 10-year survivors of testicular cancer at different ages. Risks are based on a model with ERR or EAR = $\theta \exp[\beta_1 (ax - 35) + \beta_2 \log(a/60)]$, where ax is age at testicular cancer diagnosis and a is attained age (age at observation). **A**) Modeled ERR of all solid cancers among 10-year survivors of testicular cancer as a function of age at observation and age at testicular cancer diagnosis. Parameter estimates were: $\theta = 0.93$ (95% confidence interval [CI] = 0.83 to 1.05), $\beta_1 = -0.039$ per year of age (95% CI = −0.055 to −0.024), $\beta_2 = -0.97$ (95% CI = −1.6 to −0.32). The corresponding relative risk (RR) can be derived by the addition of 1 to the ERR (e.g., if ERR = 2.0, then RR = 3.0). **B**) Modeled EAR of all solid cancers among 10-year survivors of testicular cancer as a function of attained age and age at testicular cancer diagnosis. Parameter estimates were: $\theta = 62$ per 10^4 person-years (95% CI = 54 to 70), $\beta_1 = -0.046$ (95% CI = −0.063 to −0.030), $\beta_2 = 4.4$ (95% CI = 3.7 to 5.1).

Table 3. Relative risk of second cancers in men diagnosed with testicular cancer at age 35 years according to time since testicular cancer diagnosis, initial treatment, calendar year, and histology*

	All patients†		GCT, seminoma		GCT, nonseminoma	
	No. of solid tumors	RR (95% CI)	No. of solid tumors	RR (95% CI)	No. of solid tumors	RR (95% CI)
Time since testicular cancer diagnosis (n = 40 576)						
1–4 y	233	1.2 (0.97 to 1.4)	172	1.0 (<1 to 1.3)	54	1.4 (1.1 to 1.8)
5–9 y	358	1.4 (1.2 to 1.6)	280	1.5 (1.2 to 1.8)	63	1.2 (<1 to 1.5)
10–19 y	802	2.1 (1.9 to 2.3)	587	2.2 (1.0 to 2.5)	191	1.9 (1.6 to 2.2)
20–29 y	563	2.0 (1.8 to 2.2)	407	2.0 (1.8 to 2.2)	143	2.0 (1.7 to 2.3)
30–34 y	169	1.8 (1.5 to 2.1)	133	1.9 (1.6 to 2.3)	32	1.4 (1.1 to 1.9)
≥35 y	160	1.7 (1.5 to 2.0)	115	1.8 (1.5 to 2.1)	40	1.5 (1.2 to 2.0)
All ≥10-y intervals	1694	1.9 (1.8 to 2.1)	1242	2.0 (1.9 to 2.1)	406	1.8 (1.6 to 2.0)
Initial treatment (limited to 10-y survivors of testicular cancer) (n = 9551)						
Radiotherapy alone	892	2.0 (1.9 to 2.2)	700	2.0 (1.8 to 2.2)	170	2.1 (1.8 to 2.5)
Chemotherapy alone	35	1.8 (1.3 to 2.5)	6	1.6 (<1 to 4.3)	28	1.8 (1.3 to 2.5)
Radiotherapy and chemotherapy	25	2.9 (1.9 to 4.2)	16	3.8 (2.2 to 6.0)	9	2.2 (1.1 to 3.8)
Calendar year of testicular cancer diagnosis (limited to 10- to 24-y period after testicular cancer diagnosis) (n = 14 679)						
All treatments						
1943–1974	476	1.9 (1.7 to 2.2)	350	1.9 (1.6 to 2.1)	111	2.1 (1.7 to 2.5)
1975+	399	2.1 (1.8 to 2.3)	297	2.3 (2.0 to 2.7)	91	1.7 (1.4 to 2.1)
Radiotherapy alone						
1943–1974	272	2.0 (1.7 to 2.3)	192	1.7 (1.4 to 2.0)	69	2.7 (2.1 to 3.4)
1975+	145	2.3 (1.9 to 2.8)	127	2.5 (2.0 to 3.2)	18	1.6 (1.0 to 2.5)
Radiotherapy alone: sites in-field‡						
1943–1974	146	2.7 (2.2 to 3.2)	98	2.1 (1.6 to 2.7)	41	4.0 (2.8 to 5.3)
1975+	66	2.9 (2.2 to 3.9)	60	3.4 (2.5 to 4.6)	6	1.4 (<1 to 2.9)

*The relative risk (RR) is a decreasing function of age at testicular cancer diagnosis; results are presented for age 35 years, which is the mean age of the cohort. GCT = germ cell tumor; CI = confidence interval.

†All 40 576 patients who were diagnosed with testicular cancer as a first primary cancer and survived 1 year or more are included in analyses of time since testicular cancer diagnosis. Analyses of initial treatment include 9551 10-year survivors reported to cancer registries in Denmark, Finland, and Norway and to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. Analyses of calendar year of testicular cancer diagnosis exclude patients reported to the SEER Program, because data collection did not begin until 1973. Of the 14 679 patients included in the calendar year analyses, 4386 received radiotherapy alone.

‡Restricted to sites that are usually included in infradiaphragmatic radiotherapy fields for testicular cancer: stomach, small intestine, colon, rectum, liver, gallbladder and ducts, pancreas, kidney, and bladder.

to 4.8) accounted for almost 60% of the total excess. The highest site-specific relative risks were found for cancers of the stomach, pancreas, and connective tissue, followed by cancers of the pleura and bladder, with increased risks persisting for at least 30 years for most sites. For cancers of colon, prostate, kidney, and bladder, risks remained statistically significantly elevated ($P<.05$) for 35 years (data not shown). Fourteen of 15 pleural cancers were histologically confirmed as malignant mesotheliomas. Among 10-year testicular cancer survivors, there was little evidence of an increase or decrease in relative risks with additional follow-up through four decades for most sites; exceptions were statistically significant negative trends for cancers of stomach ($P<.001$) and lung ($P<.001$) and a positive trend for kidney cancer ($P = .02$). Transitional cell carcinomas of the renal pelvis (n = 20) accounted for one-third of kidney cancers for which histologic type was specified (n = 61).

Among testicular cancer patients treated with radiation alone, relative risks for sites in typical infradiaphragmatic radiotherapy fields (RR = 2.7; 95% CI = 2.4 to 3.0) clearly exceeded those for remaining sites (RR = 1.6, 95% CI = 1.4 to 1.8). For in-field sites, statistically significantly increased risks persisted for 35 years or more (RR = 2.3, 95% CI = 1.8 to 3.0), with no evidence of decline ($P = .41$). For remaining sites, risk appeared to decrease with time since diagnosis ($P_{trend} = .005$). Among patients given radiotherapy alone, risks were significantly elevated for cancers of the stomach (RR = 4.1, 95% CI = 3.2 to 5.2), colon (RR = 1.9, 95% CI = 1.5 to 2.5), rectum (RR = 1.8, 95% CI = 1.3 to 2.5), pancreas (RR = 3.8, 95% CI = 2.7 to 5.0), lung (RR = 1.4, 95% CI = 1.1 to 1.7), pleura (RR = 4.4, 95% CI = 2.0 to 8.1), prostate (RR = 1.4, 95% CI = 1.1 to 1.8), kidney (RR = 2.8, 95% CI = 2.1 to 3.8), bladder (RR = 2.7, 95% CI = 2.1 to 3.3), malignant melanoma (RR = 1.6, 95% CI = 1.05 to 2.4), connective tissue (RR = 5.1, 95% CI = 2.4 to 9.2), and thyroid (RR = 3.1, 95% CI = 1.2 to 6.7).

There was little evidence that site-specific cancer risks differed by histologic type of testicular cancer or that the parameter quantifying the effect of age at testicular cancer diagnosis varied among sites. Overall, 698 (41.2%) of the 1694 solid cancers diagnosed 10 or more years after the diagnosis of testicular cancer were in excess. Cancers of stomach, colon, pancreas, lung, and bladder accounted for 397 (56.9%) of the 698 excess cases, with bladder cancer making the largest contribution (115 cases = 16.4%). Among patients initially given radiation alone, sites in typical infradiaphragmatic radiotherapy fields accounted for 63.7% of the excess cancers.

Cumulative risks for all solid cancers were slightly higher for seminoma patients than for nonseminoma patients (Fig. 2); for men diagnosed with seminoma or nonseminoma at age 35 years, cumulative risks were 36% and 31%, respectively, at 40 years of

Table 4. Estimated relative risk of second cancers according to time since testicular cancer diagnosis for patients diagnosed with testicular cancer at age 35 years*

	Time since testicular cancer diagnosis								No. of excess cancers (%)†
	All ≥10 y intervals		10–19 y		20–29 y		≥30 y		
Cancer site	No. obs.	RR (95% CI)	No. obs.	RR (95% CI)	No. obs.	RR (95% CI)	No. obs.	RR (95% CI)	All ≥10-y intervals
All solid tumors	1694	1.9 (1.8 to 2.1)	802	2.1 (1.9 to 2.3)	563	2.0 (1.8 to 2.2)	329	1.7 (1.6 to 1.9)‡	698§ (100)
Esophagus	26	1.7 (1.0 to 2.6)	13	2.0 (<1 to 3.8)	7	0.9 (<1 to 2.3)	6	2.1 (<1 to 4.0)	9 (1.3)
Stomach	129	4.0 (3.2 to 4.8)	64	4.9 (3.7 to 6.4)	49	4.5 (3.3 to 5.9)	16	1.9 (1.0 to 3.2)‖	88 (12.6)
Colon	153	2.0 (1.7 to 2.5)	62	1.8 (1.3 to 2.6)	52	2.1 (1.5 to 2.8)	39	2.2 (1.6 to 3.0)	66 (9.5)
Rectum/anus	101	1.8 (1.4 to 2.3)	60	2.7 (1.9 to 3.8)	22	1.3 (<1 to 1.9)	19	1.7 (1.1 to 2.6)	39 (5.5)
Pancreas	95	3.6 (2.8 to 4.6)	44	4.1 (2.8 to 5.9)	38	4.3 (3.0 to 6.0)	13	2.3 (1.3 to 3.7)	63 (9.0)
Lung	256	1.5 (1.2 to 1.7)	148	2.2 (1.7 to 2.7)	73	1.4 (1.1 to 1.8)	35	1.0 (<1 to 1.4)‖	65 (9.3)
Pleura	12	3.4 (1.7 to 5.9)	7	6.0 (2.3 to 12)	3	2.6 (0.5 to 6.6)	2	1.9 (0.4 to 6.1)	8 (1.1)
Prostate	249	1.4 (1.2 to 1.6)	88	1.1 (<1 to 1.6)	91	1.4 (1.1 to 1.8)	70	1.5 (1.2 to 1.8)	52 (7.4)
Kidney	80	2.4 (1.8 to 3.0)	29	1.7 (1.0 to 2.6)	30	2.5 (1.7 to 3.6)	21	3.0 (1.9 to 4.4)¶	43 (6.2)
Bladder	211	2.7 (2.2 to 3.1)	75	2.0 (1.4 to 2.7)	85	3.2 (2.5 to 4.0)	51	2.6 (2.0 to 3.5)	115 (16.4)
Malignant melanoma	70	1.8 (1.3 to 2.3)	43	1.9 (1.3 to 2.6)	23	2.1 (1.4 to 3.1)	4	0.8 (0.3 to 1.7)	30 (4.2)
Thyroid	16	2.3 (1.0 to 4.4)	15	4.2 (1.8 to 8.2)	1	1.0 (<1 to 3.4)	0	—	9 (1.2)
Connective tissue	19	4.0 (2.3 to 6.3)	9	3.7 (1.7 to 7.0)	9	6.1 (2.8 to 11)	1	1.6 (<1 to 5.8)	14 (2.0)
Other solid tumors#	277	1.6 (1.4 to 1.9)	145	1.5 (1.2 to 1.9)	80	1.6 (1.3 to 2.0)	52	1.9 (1.4 to 2.4)	98 (14.1)
Radiotherapy only									
All solid tumors	892	2.0 (1.9 to 2.2)	399	2.2 (1.9 to 2.5)	300	2.0 (1.8 to 2.3)	193	1.8 (1.6 to 2.1)**	387§ (100)
Sites in-field††	445	2.7 (2.4 to 3.0)	174	2.6 (2.1 to 3.2)	165	2.9 (2.4 to 3.4)	106	2.5 (2.0 to 3.0)	246 (63.7)
Other sites	447	1.6 (1.4 to 1.8)	225	1.9 (1.6 to 2.3)	135	1.5 (1.3 to 1.8)	87	1.4 (1.1 to 1.7)‡‡	141 (36.3)

*Data are restricted to those sites for which statistically significantly increased relative risks were observed in 10-year survivors of testicular cancer. The RR is a decreasing function of age at testicular cancer diagnosis; results are presented for age 35 years, which is the mean age of the cohort. RR = relative risk; CI = confidence interval; Obs. = observed number of cases.

†Percent contribution to the total excess is shown in parentheses; percentages may not sum to 100 due to rounding.

‡P_{trend}(negative) = .007.

§Obtained as sum of site-specific excesses.

‖P_{trend}(negative)<.001.

¶P_{trend}(positive) = .02.

#Includes 172 tumors for which site was specified and 105 tumors of unknown or ill-defined primary site (refer to Appendix Table 2 for complete list of solid tumors for all periods).

**P_{trend}(negative) = .013.

††Restricted to those sites which are included in typical infradiaphragmatic radiotherapy fields for testicular cancer: stomach, small intestine, colon, rectum, liver, gallbladder and ducts, pancreas, kidney, and bladder.

‡‡P_{trend}(negative) = .005.

follow-up compared with 23% for the general population. Cumulative risk at any given attained age increased with decreasing age at testicular cancer diagnosis. If estimated trends with age at testicular cancer diagnosis and attained age were to continue, a patient diagnosed with seminoma at age 20 years would have a cumulative risk of solid cancers of 47% by age 75 years compared with 36% and 28% for patients diagnosed at age 35 years or 50 years, respectively.

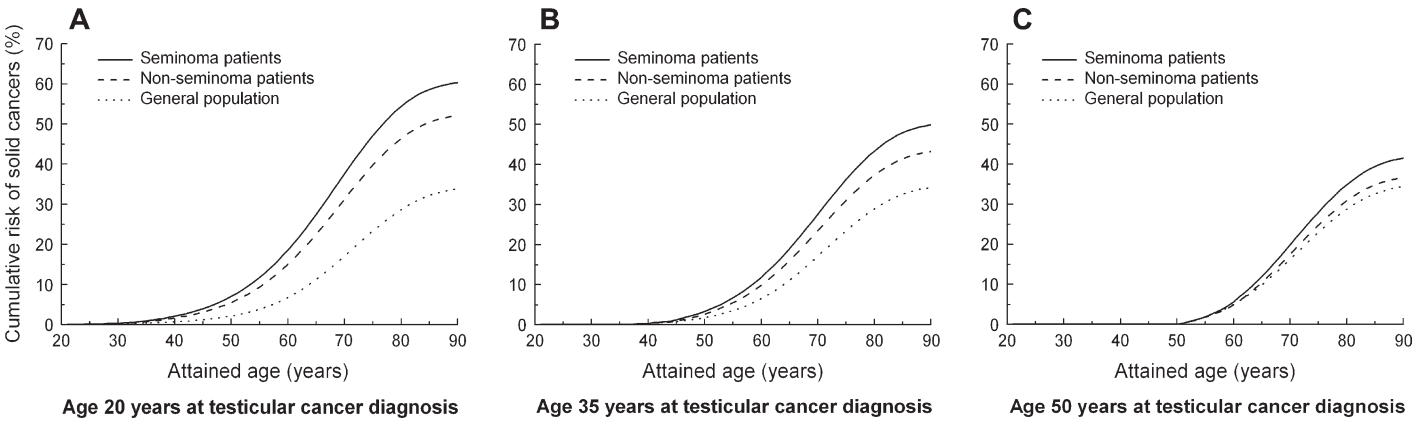

Fig. 2. Cumulative risk (%) of developing a second solid cancer for men with seminomas and nonseminomatous germ cell tumors according to age at testicular cancer diagnosis and attained age. Risks beyond age 60 years for men diagnosed with testicular cancer at age 20 years, or beyond age 75 years for men diagnosed with testicular cancer at age 35 years represent extrapolation of estimated trends.

Discussion

This is, to our knowledge, the largest study to date of testicular cancer patients; it includes more than 7800 20-year and 2065 30-year survivors in a population-based setting. By analyzing more than 2200 solid cancers, we were able to evaluate risk in relation to time since diagnosis of testicular cancer (over four decades), age at testicular cancer diagnosis, attained age, testicular cancer histology, type of initial therapy, and calendar year. New findings include the strong age dependence of excess cancers, the persistence of statistically significantly increased risks of cancer for at least 35 years after testicular cancer diagnosis, and statistically significant associations between the receipt of chemotherapy and the risk of a second cancer. We also identified, to our knowledge for the first time, statistically significant excesses of cancers of the pleura and esophagus. The overall constellation of increased site-specific risks of solid tumors was similar for seminoma and nonseminoma patients. Nonseminoma patients treated in more recent decades (1975–2001) had lower risks of solid tumors than those treated in earlier periods.

In contrast to most cohort studies of testicular cancer survivors *(7–9,12,14,36–38)*, multivariable modeling was used to evaluate solid tumor risks. Adjustment for age at testicular cancer diagnosis was especially important, because this factor was related both to solid cancer risk and to other variables such as tumor histology and time since diagnosis. A particularly striking finding was the strong increase in both the ERR and EAR of solid tumors with decreasing age at testicular cancer diagnosis. A patient treated for seminoma or nonseminoma at age 20 years, for example, had an ERR of solid cancers that was about three times higher than that of a patient treated at age 40 years. The ERR declined with attained age, indicating that the EAR did not increase as rapidly as background rates. Nevertheless, the EAR showed a strong increase with attained age over the 40-year follow-up period included in our study. Although it is not known whether risks continue to increase beyond 40 years, the finding could have important implications regarding future cancer risks, especially for young testicular cancer patients. For example, a patient diagnosed with seminoma at age 20 years would be projected to have a cumulative risk of solid cancers of almost 50% by age 75 years.

Several studies of testicular cancer patients, but not all *(39)*, have identified statistically significantly increased risks for cancers of gastrointestinal and genitourinary tracts and other sites. A comprehensive discussion of site-specific risks was included in a prior survey *(9);* in this study, we supplement this number with an additional 11 733 testicular cancer patients and 1034 new solid cancers. We focus below on long-term cancer risk for selected sites included in typical radiotherapy fields for testicular cancer, with consideration given to organ doses received during these treatments (Appendix Table 1).

Infradiaphragmatic Cancers (Bladder, Stomach, Pancreas, or Kidney)

Among 10-year survivors of testicular cancer initially given radiotherapy, the relative risks of solid tumors at sites included in typical infradiaphragmatic fields were considerably higher than those at sites not in the field (Table 4). In particular, elevated risks of bladder cancer were described previously *(8,9)*, with extended follow-up now showing no evidence for a diminution in risk, even 35 years or more after treatment. During iliac radiotherapy for testicular cancer, ipsilateral portions of bladder are exposed to full-dose irradiation, whereas remaining sites receive scattered dose. Given the statistically significant dose–response relation evident for radiation and bladder cancer *(40)*, reductions in field size and radiotherapy doses for testicular cancer *(10,11)* may translate into decreased risks in the future.

Excess stomach cancers after treatment for testicular cancer *(7,9,41)* are consistent with the large doses of radiation received by this organ during abdominal radiotherapy. Although increased risks of stomach cancer persisted for at least 30 years, the magnitude of excess relative risk decreased statistically significantly with extended observation time. The stomach was the only infradiaphragmatic organ for which such a temporal pattern was evident, with additional follow-up needed to confirm this finding.

Sparse data indicate that pancreatic cancer may follow therapeutic amounts of radiation *(42,43)*, with little evidence for induction at lower doses *(44,45)*. Radiotherapy for testicular cancer can result in pancreas doses of up to 28 Gy. Statistically significant excesses of pancreas cancer, which have been observed in several surveys of testicular cancer patients *(6–9,46)* but not others *(7,8,37,38)*, are now confirmed, with excesses persistent for more than three decades.

Excess relative risks of kidney cancer continued to increase 10 years or more after testicular cancer diagnosis. During para-aortic radiotherapy for testicular cancer, medial sections of kidney parenchyma and renal pelvis receive radiation doses up to 10 Gy, which may account for the sizable proportion of transitional cell carcinomas of the renal pelvis that we observed. Although kidney cancer is not universally regarded as radiogenic *(45)*, radiotherapy for cervical cancer (average kidney dose = 2 Gy) resulted in statistically significantly increased risks for 30 years or more *(47)*. It is not clear whether cytotoxic and/or radiosensitizing drugs might contribute to excess kidney cancers in long-term testicular cancer survivors *(48–50)*.

Supradiaphragmatic Cancers (Esophagus, Pleura, or Lung)

To our knowledge, this is the first report of statistically significantly increased risks of cancers of esophagus and pleura among testicular cancer patients. Our results should be considered in relation to the supradiaphragmatic radiotherapy fields frequently applied in the past *(5,20,51)*, which delivered an average dose of 21.5 Gy or more to the esophagus. Excess esophageal cancers have been reported after therapeutic chest irradiation for breast cancer *(52)* and Hodgkin lymphoma *(53)*. Previous case reports *(54)* record the occurrence of pleural mesothelioma after chest radiotherapy for Hodgkin lymphoma, breast cancer, and testicular cancer (one patient). Neugut et al. *(55)*, in an analysis of SEER Program data, found a slight, non–statistically significant risk of mesothelioma after radiotherapy, based on only two cases among women with breast cancer. Our series, with 14 mesotheliomas, is the largest yet

reported. Among men initially treated with radiotherapy alone, the risk of pleural cancer was increased (RR = 4.0, 95% CI = 2.0 to 8.1), thus adding to the mounting evidence that very high doses of radiation might be causally related to cancers at this site.

Lung cancer accounted for the fourth-largest number of excess solid tumors. Hoff Wanderas et al. *(8)*, whose patients are included in this series with updated follow-up, reported a statistically significantly increased twofold to fivefold risk of lung cancer (28 cases) after testicular cancer, most often after chest irradiation. Similarly, van Leeuwen et al. *(7)* observed non–statistically significant 2.5-fold lung cancer excesses (four cases) among a subgroup of 141 testicular cancer patients given mediastinal radiotherapy. During such chest radiation, medial portions of lung received up to 16.8 Gy. By extrapolating from our findings in a previous case–control study *(48)*, it can be estimated that about 16% of testicular cancer patients in this series may have received chest radiotherapy. Statistically significant dose-dependent risks of lung cancer have been observed among patients given thoracic radiotherapy for Hodgkin lymphoma *(56–58)* and breast cancer *(59)*. Whether tobacco use might contribute to the lung cancer findings is unknown, but there is no reason to believe that the prevalence of smoking in testicular cancer patients exceeds that in the general population *(60)*.

Other Findings

The decrease in the risk of solid tumors for nonseminoma patients treated since 1975 compared with those treated in prior calendar years likely reflects several factors, including the introduction of effective chemotherapy; the decreased use of radiotherapy, with lower doses and smaller fields; and the application of surveillance policies *(61,62)*. Extended follow-up, however, is needed to determine whether lowered risks will continue throughout the third and fourth decades after treatment. The continued use of radiotherapy after 1975 in most seminoma patients *(63)* may be the reason why similar decreases in risk were not observed in this group; there is no obvious explanation for the apparent increase in risk, and this may represent a chance finding, given the large number of comparisons that were made.

Platinum-based chemotherapy for testicular cancer has been linked with statistically significant dose-dependent increased risks of leukemia *(48)*, and sparse data have suggested associations with solid cancers *(7,8,12)*. We document that treatment of testicular cancer with chemotherapy alone is associated with statistically significantly increased risks of solid cancers, but analytic studies will be required to quantify treatment-specific risks and determine their causes. Platinum is retained in the human body long after the completion of treatment *(64–66)* and causes solid tumors in preclinical studies *(50)*.

From small numbers and former treatment schedules, it has been suggested that chemotherapy for testicular cancer enhances the risk of radiotherapy-associated solid tumors *(8,36)*. Testicular cancer patients treated with chemotherapy and radiotherapy in the current series experienced a larger risk of solid tumors than those given radiotherapy alone, but the difference was not statistically significant. Few patients (n = 782), however, received combined modality therapy.

Comment

Our results should be viewed within the context of the strengths and limitations of cancer registry–based data. Population-based studies minimize the selection bias inherent in hospital or clinical series and allow evaluation of site-specific second cancer risk among many patients. Underreporting of second cancers among patients who emigrate from registry catchment areas is unlikely in Nordic countries, which have nationwide registration, but it is a concern in more localized North American registries, and we adjusted the analysis for this possible shortcoming.

Another limitation of this study is that treatment designation represents only initial management, without consideration of salvage treatment. Thus, misclassification may serve to dampen any differences between therapeutic categories. Further, radiation doses to specific organs of individual patients were not computed, and inferences were made on the basis of typical treatments. Details of the chemotherapy regimens also were not known. In any analysis of multiple primary cancers, the sizable number of comparisons may produce some statistically significant associations by chance alone.

Although the discussion above focuses on treatment as the primary explanation for the observed excesses, it should be kept in mind that elevated patterns of solid tumor risk may also reflect the influence of natural history, diagnostic surveillance, and shared etiologic factors *(67)*. Several reports *(12,36,68)* conclude that testicular cancer patients do not appear at inherently elevated risk of solid tumors. One promising testicular cancer susceptibility gene has been mapped to chromosome Xq27 *(69)*. Identification and characterization of such a gene(s) may facilitate elucidation of any contribution of shared genetic susceptibility to excess tumors in testicular cancer patients. Treatment can probably explain much of the observed excess in this study, an interpretation that is supported by the lower risks in the first 10 years of follow-up, when radiation-related cancers would be infrequent, and by the especially high risks for cancer sites in standard radiotherapy fields.

Nevertheless, our results provide a reasonable gauge of the risk of solid tumors among long-term testicular cancer survivors and serve to heighten clinician and patient awareness of this risk. Testicular cancer survivors should be encouraged to adopt practices that are consistent with a healthy lifestyle, including smoking cessation *(70)*; to seek medical consultation for any persistent changes in health status; and to follow screening guidelines applicable to the general population *(71)*. In future investigations, radiation doses to second cancer sites should be quantified with the cumulative doses of specific cytotoxic drugs to clarify the contribution of treatment effects. Future evaluations should also assess interactions of therapy with other genetic and environmental determinants of site-specific cancer risk *(67)*.

Despite the statistically significantly increased long-term risk of second solid tumors, it is clear that the remarkable gains in survival provided by treatments for testicular cancer far outweigh the risk of this serious late effect, and generalization of our results to modern practice should be undertaken with caution. Given current modifications in treatment that result in lower radiation doses *(10,11,72,73)*, solid tumors in the future will probably have considerably less impact on the lives of testicular cancer survivors, although careful follow-up is necessary to reliably quantify long-term risk.

Appendix Table 1. Estimated dose to selected organs after radiation treatment for testicular cancer*

Organ	Avg total dose received by organ or site, Gy			
	Infradiaphragmatic radiotherapy			
	Para-aortic and iliac fields			
	50 Gy	30 Gy	Para-aortic field only, 20 Gy	Chest radiotherapy, mediastinal field, 30 Gy
Esophagus				
Total	1.6	1.0	0.4	21.5
Lower third	4.5	2.7	1.1	27.9†
Stomach	24.7	14.8	10.0	1.7
Small intestine	22.5	13.5	4.7	0.2
Colon‡	2.8–50	1.7–30	0.5–9.4	0.2
Rectum	38.8	22.8	0.2	0.1
Liver	15.9	9.5	7.0	2.3
Gallbladder and ducts	8.0	4.8	7.3	0.7
Pancreas	28.0	16.8	12.9	1.2
Lung	1.1	0.6	0.3	11.9§
Prostate	7.1	4.3	0.1	0.05
Kidneys				
Total‖	7.0	4.2	5.7	0.8
Medial sections	10.2	6.1	9.5	0.9
Bladder	17.0	10.2	0.2	0.06
Thyroid	0.09	0.06	0.03	15.5¶

*Radiation doses to target organs were estimated with methods as described by Stovall et al. *(21)*. Treatment simulation was based on standard anterior–posterior (AP)/posterior–anterior para-aortic and iliac fields (total administered doses of 50 Gy and 30 Gy) or para-aortic fields only (20 Gy) *(22)*. Mediastinal radiotherapy included the left supraclavicular fossa *(20)*. Although representative fields during the study period are shown above, radiation doses for individual patients are not available but likely fall within the range of values presented. Gy = gray.

†Average doses to the upper and middle third of the esophagus are 8.4 and 28.3 Gy, respectively.

‡The range represents doses to different segments of the colon (ascending, transverse, descending, and sigmoid).

§Average doses to the medial and lateral parts of the lung are 16.8 and 1.2 Gy, respectively.

‖For para-aortic and iliac fields, doses are listed for the unblocked kidney. Doses to the blocked kidney are 6.0 Gy and 3.6 Gy for treatment doses of 50 Gy and 30 Gy, respectively.

¶Average doses to the left and right lobes of the thyroid are 25.2 and 5.7 Gy, respectively.

Appendix Table 2. Observed number of second cancers, observed-to-expected ratio, and excess number (observed minus expected) among 40 576 1-year survivors of testicular cancer*

Type of cancer	No. observed	Observed-to-expected ratio (95% CI)	No. of excess solid tumors†
All solid tumors‡	2285	1.41 (1.35 to 1.47)	665.7
All buccal	79	1.13 (0.89 to 1.41)	9.0
Esophagus	38	1.44 (1.02 to 1.98)	11.7
Stomach	155	2.16 (1.84 to 2.53)	83.4
Small intestine	19	2.60 (1.56 to 4.06)	11.7
Colon	192	1.36 (1.18 to 1.57)	51.3
Rectum/anus	135	1.46 (1.23 to 1.73)	42.8
Liver	23	1.08 (0.69 to 1.63)	1.8
Gallbladder and ducts	16	1.58 (0.90 to 2.56)	5.9
Pancreas	115	2.30 (1.90 to 2.76)	65.0
Larynx	34	1.13 (0.78 to 1.57)	3.8
Lung	345	1.19 (1.07 to 1.32)	54.4
Pleura§	15	2.80 (1.57 to 4.62)	9.6
Breast	3	1.21 (0.24 to 3.53)	0.5
Prostate	357	1.05 (0.95 to 1.17)	18.1
Kidney‖	106	1.42 (1.16 to 1.72)	31.4
Bladder	258	1.93 (1.70 to 2.18)	124.5
Malignant melanoma	122	1.48 (1.23 to 1.77)	39.8
Eye	5	0.91 (0.29 to 2.11)	−0.5
Brain and central nervous system	66	1.14 (0.88 to 1.45)	8.0
Thyroid	30	2.17 (1.46 to 3.10)	16.2
Bone	7	1.66 (0.66 to 3.42)	2.8
Connective tissue	33	2.65 (1.83 to 3.73)	20.6
All other¶	132	1.69 (1.42 to 2.01)	54.0

*Unadjusted observed-to-expected (O/E) ratios were calculated by use of a standard approach *(9)*. Site-specific O/E ratios did not differ statistically significantly between seminoma patients and patients with nonseminomatous germ cell tumors. CI = confidence interval.

†Observed minus expected.

‡Numbers exclude contralateral testicular cancers. Of the 2285 testicular cancer patients who developed a second solid tumor, 192 subsequently developed a third or higher-order invasive cancer (n = 242 cases).

§Fourteen of 15 pleural cancers were histologically confirmed as malignant mesothelioma. For one patient, histology was not specified.

‖Histologic subtype was specified for 82 cancers (59 renal cell carcinoma and 23 transitional cell carcinoma).

¶Includes all solid tumors not itemized in table (i.e., those of unknown or ill-defined primary site).

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